UNIVERSITY OF SPLIT

SCHOOL OF MEDICINE

Daniel Leidinger

ADHERENCE OF PATIENTS WITH DIABETES AND HYPERTENSION

Diploma thesis

Academic year:

2017/2018

Mentor:

Assoc. Prof. Ozren Polašek, MD, MPH, PhD

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1. INTRODUCTION

Diabetes and hypertension are important causes of mortality, morbidity, and health-system costs in the world. These diseases due to their chronic nature require a high degree of self-monitoring and -administration of treatment from the patient, leading to suboptimal levels of adherence to the treatment regimen.

1.1. Definition of adherence

The WHO defines adherence as: "The extent to which the patient's behavior – taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider." (1).

1.2. Importance of adherence

The term "adherence" is the preferred term today compared to "compliance" which was used most often in the past. Compliance is associated with a paternalistic role of the treating health professional, in the sense of not following the drug regimen prescribed by the doctor, whereas adherence is based on the therapeutic alliance between patient and treating physician and thus explicitly refers to responsibilities on both sides. The main goal of any prescribed medical therapy is to reach a certain desired outcome in the patient. In order to achieve this desired result many therapies require a certain degree of self-management of the patient. Adherence to the therapy is not restricted to the patient taking his medication but also often includes other demanding factors like sticking to a diet, exercising and making life style changes in general (2).

Good adherence to a beneficial drug therapy is associated with reduced mortality compared to poor adherence (3).

Problems with adherence are observed in all situations where the self-administration of treatment is required, regardless of type of disease, disease severity and accessibility to health resources. Especially in chronic diseases patients experience difficulties to stick to their recommended regimens with an estimated adherence rate of 40-50% (compared with 70-80% for short term therapy). This leads to suboptimal disease control, causes medical and psychosocial complications of disease, reduces patients' quality of life, and wastes health care resources. Poor adherence is the primary reason for suboptimal clinical benefit (1,2).

1.3. Factors influencing adherence

A large number of studies have been conducted over the years to find out factors that can have an impact on adherence. A systematic review that was published in 2008 searched the Medline database from 1970 to 2005 to identify relevant factors relating to therapeutic adherence. They found numerous factors and they are somewhat intertwined with each other, however they can be subdivided into five main categories: patient-centered factors, therapy-related factors, social and economic factors, healthcare system factors and disease factors (2).

Patient centered factors include demographic factors like age, ethnicity, gender, education and marriage status and psychosocial factors like beliefs, motivation and attitude. Furthermore, patient centered factors are composed of the patient-prescriber relationship, health literacy, patient knowledge, physical difficulties, tobacco smoking or alcohol intake, forgetfulness and a history of good compliance (2). Therapy-related factors consist of the route of administration, treatment complexity, the duration of the treatment period, medication side effects, the degree of behavioral change required, taste of the medication and requirements for drug storage (2). Healthcare system factors are lack of accessibility, long waiting time, difficulty in getting prescriptions filled and unhappy clinic visits (2). Social and economic factors are comprised of the inability to take time off work, cost and income and social support (2). Disease factors are disease symptoms and the severity of the disease (2).

Of course, these factors differ on the effect they have on adherence, with some of them having inconsistent and even contradictory impact.

1.4. Diabetes Mellitus

Diabetes is a chronic disease characterized by high levels of blood sugar, resulting from insufficient insulin secretion, disturbed insulin action, or both. The body needs insulin to enable the cells to take up sugar from the blood and use it as an energy source or to convert it into fat. If unable to do so, elevated blood sugar levels eventually lead to damage to organs, blood vessels and nerves. Diabetes is highly prevalent with 422 million adults living with the disease in 2014 worldwide compared to 108 million in 1980. The main causes for this drastic increase are considered to be an aging population, poor diet, obesity and a sedentary lifestyle (1).

1.5. Types of diabetes

There are three main types of diabetes, Diabetes type 1 and 2 and gestational diabetes. Type 1 diabetes is the result of destruction of pancreatic beta cells, which are responsible for the production of insulin. The loss of beta cells is most often caused by an autoimmune reaction but can also be idiopathic (4). As a result, blood insulin levels are continuously low and the blood sugar level increases. The disorder precipitates in genetically susceptible individuals presumably triggered by environmental factors like enteroviruses. The genes associated with type 1 diabetes include HLA, insulin, PTPN22, IL2Ra, and CTLA4 (4). This form of diabetes accounts for only 5–10% of all cases of the disease (5).

Type 2 diabetes is caused by a combination of resistance to insulin action by the target cells and an inadequate compensatory insulin secretory response by the pancreas (5). The main factors leading to the disease are excessive body weight and insufficient exercise, but there also is a genetic component (6). It is the most prevalent form of the disease accounting for about 90% of all cases of diabetes (7).

Gestational diabetes is hyperglycaemia with onset or recognition during pregnancy. It is found in 2–10% of pregnancies and may disappear after delivery. However in 5–10% of cases it progresses to diabetes mellitus type 2 (6).

1.6. Complications and burden of disease

Especially if left untreated or if poorly controlled, diabetes can lead to a series of complications including diabetic ketoacidosis, kidney failure, amputations, blindness, heart attacks and stroke among many others. According to estimations of the WHO 1.6 million deaths annually can be directly attributed to Diabetes. The treatment costs of diabetes amount to 825 billion dollars annually worldwide (8).

1.7. Prevention and treatment of diabetes:

There are no known prevention measures for Diabetes type 1 (6).

Type 2 diabetes however can often be prevented or at least delayed by a change in lifestyle. Consuming a healthy diet, exercising, maintaining a normal body weight and avoiding tobacco use all decrease the risk of developing the disease (6).

Early diagnosis is a key component in the treatment of diabetes. The longer a person lives with untreated diabetes the poorer the outcome is likely to be (9).

The main goal of diabetes treatment is to maintain the blood sugar at physiologic levels, thus avoiding acute complications like hypo- and hyperglycemia and chronic complications like heart disease (10).

In Type 1 diabetes insulin therapy is always required as well as dietary changes and exercise (11).

Type 2 diabetes may be managed with insulin, weight reduction, dietary changes and non-insulin medications like the oral hypoglycaemic agent metformin (12).

Most patients with type 2 diabetes are not able to control their blood sugar level with diet and exercise alone and require the introduction of pharmacotherapy. At this point a monotherapy with an oral hypoglycaemic agent is commonly introduced. In the case that the blood sugar control is still not effective enough or due to progression of the disease, more medications can be added as part of a polytherapy regimen. As a last step injectable treatments are introduced (13).

Regular screenings for retinopathy and kidney disease, blood lipid control and foot care are also helpful methods of reducing both complications and costs of treatment (9). HbA1c can be used as an indicator for both the management of diabetes and as a predictor for the clinical outcomes.

1.8. Adherence in diabetes

The proper treatment of diabetes requires a lot from the patient. Taking medicine, self-monitoring of blood sugar, sticking to dietary restrictions, regular foot care, exercise and ophthalmic examinations are important parts of the treatment regimen (1).

Due to non-compliance with these factors only 28% of patients treated for diabetes in Europe achieved good glycemic control (14). This makes poor adherence to recognized standards of care the main cause of development of complications of diabetes and their associated costs (1).

Studies show that there is a poor correlation between the adherence to different components of the treatment regimen (15). Because of this we will analyse the different treatment components separately.

1.8.1. Monitoring of glucose

There are two available methods, self-monitoring of blood glucose (SMBG) and continuous glucose monitoring (CGM). Glucose monitoring is an important part of diabetes management and a key component in the prevention of diabetes related complications. It

helps patients to maintain healthy blood sugar levels and to recognize and correct abnormal values (16). A study of children and adolescents with type 1 diabetes showed that increased number of SMBG checks in the range of 0 to 5 daily was significantly associated with reduced HbA1C (17).

For patients on insulin therapy the American Diabetes Association Practice Guidelines recommend using SMBG prior to meals and snacks, postprandially, at bedtime, before exercise, when they suspect low blood glucose, after treating low blood glucose, and prior to critical tasks such as driving (18). This usually results in 6–10 checks per day (19).

A large study found SMBG adherence rates to be as low as 44% for adults with T1DM and 24% for adults with T2DM (16).

1.8.2. Exercise and Diet

The adherence to treatment recommendations for exercise and diet is very difficult to assess. This is because of the individuality of treatment plans.

An appropriate diet can be a powerful method to prevent and reverse diabetes type 2 (20).

A Canadian cross sectional study with 80 participants with type 2 diabetes found an overall good adherence but overall daily intakes of sodium and saturated fat exceeded the nutrition therapy guidelines that were used (21).

Physical activity is considered an important intervention to achieve good glycaemic control in Type 2 diabetes. However adherence to long-term exercise programs varies widely between 10% and 80% (22).

1.8.3. Oral hypoglycemic agents (OHAs)

Studies have proved that there is an inverse relationship between taking a prescribed oral hypoglycemic agent and the HbA1c level (23). Adherence to OHA therapy ranged from 36% to 93% in an analysis of 11 retrospective studies (13). No difference in compliance was found for patients exclusively on OHA therapy whether they were on monotherapy or on combination therapies with various OHAs (24).

1.8.4. Insulin

Non-adherence to insulin is associated with increased mortality. In retrospective insulin studies in subjects with type 2 diabetes the non-adherence rates ranged from 20% to 38% (25).

A study of 1,099 patients with type 2 diabetes in Scotland found the highest compliance among patients taking only insulin with 67%. The lowest compliance was 39% in patients taking insulin together with an oral hypoglycemic agent (13).

1.9. Hypertension

Hypertension or high blood pressure is a long term medical condition characterized by an elevated pressure in the vascular system. In adults it is defined as either systolic or diastolic blood pressure that is consistently higher than a predetermined value (usually 130–140/90 depending on the guidelines (26)). It is usually asymptomatic but is a serious risk factor for cardiovascular disease.

The prevalence of the disease is continuously rising with 1 billion living with the condition in 2008 compared to 600 million in 1980 (6). Due to this high number of affected individuals, hypertension is a huge contributor to the burden of disease and to heath care costs. It is estimated that 9.4 million deaths annually can be attributed to high blood pressure, including 45% of deaths due to heart disease and 51% of all terminal stroke cases (6). This makes hypertension the leading global risk factor for mortality in the world (27).

1.10. Types of hypertension

Hypertension is classified as either primary or secondary. 90–95% of cases are primary hypertension, caused by nonspecific lifestyle and genetic factors. The most common risk factors are increased salt intake, high BMI, smoking and alcohol consumption (28,29), (30). Secondary hypertension is high blood pressure due to an identifiable cause like endocrine diseases, kidney diseases, and tumors, or as a side effect of medications (31).

1.11. Treatment of hypertension

The goal of hypertension treatment is to lower increased blood pressure in order to protect the patient from complications like heart disease, stroke and vascular disease. The target blood pressure usually ranges between 140–160/90–100 mmHg for the general population (32).

1.11.1. Non-pharmacological management

Life style changes are an important part in the treatment of hypertension and should be the initial approach to hypertension management. In some cases of increased blood pressure, a change in diet, physical exercise, weight loss and stress management might be the only

treatment necessary. Even when the treatment requires the use of medication these changes are still beneficiary and recommended. Dietary changes include reducing salt and increasing potassium intake and avoiding alcohol (33).

A randomized controlled trial of 459 adults showed that the DASH diet, a diet rich in fruits, vegetables, and low-fat dairy foods with reduced intake of saturated fats, total fat, and cholesterol, significantly reduced both systolic and diastolic blood pressure (34).

1.11.2. Medications

There are various pharmaceutical agents available for the treatment of high blood pressure. The first line medications include thiazide diuretics, beta-blockers, dihydropyridine calcium channel blockers (CCB), angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARB). They can be used as monotherapy or polytherapy. For most patients however one medication is not enough to control their hypertension (35).

1.12. Adherence in hypertension

More than 50% of patients being treated for hypertension drop out of care completely within a year of diagnosis. Of those continuing with treatment only about 50% take at least 80% of their prescribed medications. This amounts to about 75% of patients with diagnosed hypertension not achieving optimum blood-pressure control because of poor adherence (1).

A meta-analysis of 21 randomized controlled studies investigating measures of promoting adherence in antihypertensive therapy using different approaches showed an improvement in adherence in 13 studies or 60% of patients. Out of these 13 randomized controlled trials with significantly improved adherence, 12 showed additional significant positive effects on antihypertensive treatment end results (36).

1.12.1. Life style changes

A study that tried to assess the prevalence of adherence to self-management activities among hypertensive patients in terms of adherence to antihypertensive medications and lifestyle modifications found the overall adherence to be only 23%. This included diet, exercise, smoking cessation, and moderation of alcohol consumption (37). However, adherence to the different factors varies widely between different countries. This could be explained with the large differences in habits and behaviors across the globe (1).

1.12.2. Diet

Dietary adherence was only 22.5% in a study of 400 hypertensive patients. The most important negative predictors were peer influence, social gatherings, lack of support and lack of belief in the effectiveness of dietary treatment. The most effective way to increase adherence was found to be counseling (38).

1.12.3. Exercise

Adherence to exercise recommendations range between 31 to 51.9%. The English longitudinal study of aging found that participants with reported hypertension have lower physical activity levels compared to normotensive participants (39).

1.12.4. Pharmacotherapy

Adherence to pharmacotherapy for hypertension ranges between 50 and 70% depending on duration of follow-up, methods of assessment of adherence, drug regimens used in different studies and differences among the studied population. The WHO estimates that between 16 to 50% of patients with hypertension discontinue their antihypertensive medications within the first year of treatment and among those who continue their therapy in the long term, missed doses of medication are common. Good adherence with prescribed antihypertensive medication has been associated with improved blood pressure control and a risk reduction for stroke (30–43%) and myocardial infarction (15%) while suboptimal adherence is the main factor contributing to the burden of uncontrolled hypertension (1).

Studies have shown that measures to simplify medication therapy schemes, for example reducing the number of pills taken per day, are the most effective single measures to improve adherence. Combination therapy has been proofed to have a better efficacy and tolerability compared to monotherapy while suboptimal treatment tolerability profile and a high pill burden negatively affect adherence. Current hypertension treatment guidelines recommend fixed-dose combination therapy to provide well-tolerated and efficacious antihypertensive therapy with a low pill burden (40).

In our study we will try to identify characteristics that lead to better adherence in a large population-based sample from Dalmatia, namely in the populations of Vis, Korčula and Split. Additionally, our goal is to provide an overview of the proportion of individuals with undiagnosed diabetes or hypertension and those with known but poorly controlled disease.

2. AIMS AND HYPOTHESES

2.1. Aims

The aim of this study was to identify individuals with undiagnosed diabetes/hypertension and those with known but poorly controlled diabetes/hypertension in a large population-based sample from Dalmatia. We further tried to determine characteristics and traits that were associated with a higher degree of adherence.

2.2. Hypotheses

1. Older age, male gender, a lesser degree of education and lower subjective material status are associated with poorly controlled diabetes/hypertension.
2. Subjects living on the islands of Korčula and Vis are more likely to have undiagnosed diabetes/hypertension than subjects living in the city of Split.

3. MATERIALS AND METHODS

This study was based on a subsample of the 10,001 Dalmatians project, which is the largest research-oriented biobank in Croatia. The main objective of this program is to create a comprehensive resource for the study of genetic, environmental and social determinants of health and diseases with emphasis on chronic diseases, which are the leading cause of death in Croatia and other developed countries (41).

3.1. Subjects

For the purpose of this study, we accessed the data of all subjects recruited in the islands of Vis and Korčula, as well as those from the city of Split (Figure 1). The recruitment scheme was based on nearly systematic invites of the island populations (for the islands Korčula and Vis), while subjects from the city of Split were recruited in convenient sampling, aiming to reach a sample size of a thousand, and serving as the mainland control for the island populations.

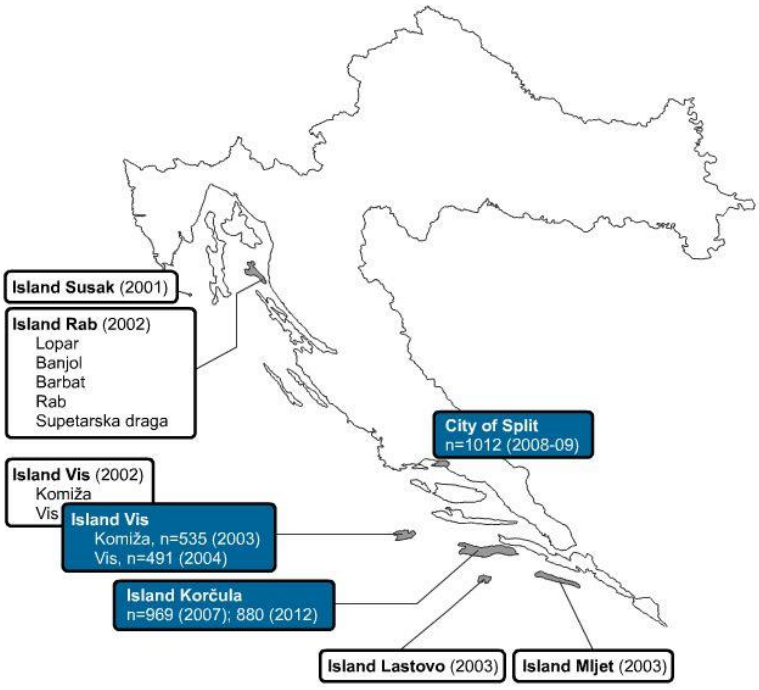

Figure 1. The map of the 10,001 Dalmatians project sites

3.2. Measurements

The assessment of blood pressure was based on two measurements in the sitting position, after at least 10 minutes of resting. The two measurements were then entered into the analysis, but the final blood pressure value was based on the double weighting of the second measurement (systolic, measurement1+ systolic, measurement2+ systolic, measurement2)/3. The cut-off values were set at 140 mmHg for systolic and 90 mmHg for diastolic blood pressure. In addition, all subjects who had a medical history of hypertension or were taking any of the hypertension-related medication were also considered to be hypertensive.

In a similar way, all subjects who had serum fasting glucose levels over 6.5 mmol/L OR had HbA1c levels above this cut-off value were considered to have measured diabetes. In addition, we considered all those who had diabetes in their medical records OR were taking any diabetes-related medication as those with positive medical records for diabetes. All glucose and HbA1c measurements were performed by the accredited laboratory (Salzer or Breyer, both located in Zagreb, Croatia). All blood samples were taken after an overnight fasting period, into 9 mL EDTA tubes, which were centrifuged in a cooled centrifuge and stored at -80°C until the analysis was performed.

Besides measurements, we also used a few survey-based questions. These were related to socioeconomic status. A total of four variables were used – a subjective perception of the individual socioeconomic status, objective perception (measured by the amount of HRK that the person earns per month), years of schooling (number of completed classes) and material index, a composite index of 16 variables that was developed for the purpose of assessing this population.

3.3. Classification

The classification above allowed us to classify all the subjects into four groups: (a) diagnosed, properly treated, (b) diagnosed, improperly treated, (c) incident - newly diagnosed and (d) healthy - undiagnosed. In the similar pattern as the contingency table, options (a) and (d) were considered as reference points, while (b) and (c) were considered as indicators of problems in health care, as both options should ideally be set at zero value. Option c indicates failure to properly diagnose diseased individuals, while option b indicates failure of the health system (or subject) to properly manage their disease. Both of these classifiers were used as the primary outcome variable, and they were the focus of this thesis.

3.4. Statistical analysis

The statistical analysis was based on descriptive and analytic methods. The numerical variables were reported as means and standard deviations, while categorical ones were based on absolute numbers and percentages. Analysis of variance was used in the numeric data analysis for three cohorts. Chi-square test was used in the analysis of categorical variables, either with one or two degrees of freedom, depending on the number of analysed groups. Logistic regression model was used in the final analytic step, in order to allow the multivariate model development, encompassing multiple inputs and allowing for the simultaneous estimation of their effect. All analyses were performed using SPSS v 21 (IBM SPSS, Armonk, NY, USA), with significance set at $P<0.050$.

4. RESULTS

This study encompassed a total of 4,851 subjects, from three cohorts of the 10.001 Dalmatians – the islands of Vis and Korčula and the coastal city of Split (Table 1). There were significant differences between the cohorts, indicating a higher share of men and an older average age in the Vis sample, and generally a better socio-economic status in Split (Table 1).

Table 1. Three samples breakdown according to the basic demographic variables

Variable*	Vis (n=1,029)	Korčula (n=2,782)	Split (n=1,012)	*P*
Sex/Men; n (%)	427 (41.5)	1,023 (36.8)	395 (39.0)	0.012
Age (years)	55.76±15.57	54.20±15.81	50.28±14.42	<0.001
Years of education	9.99±3.59	10.94±3.22	13.14±3.01	<0.001
Social status, subjective	3.02±0.77	3.13±0.70	3.33±0.70	<0.001
Social status, objective	n/a	3.32±1.42	4.25±1.42	<0.001
Material status, index	9.45±2.74	10.24±2.65	11.30±2.46	<0.001

*Expressed as mean ± standard deviation

The initial analysis of blood pressure and diabetes in the three cohorts indicated widespread significant differences, with a generally better situation in Split and a worse situation in Vis (Table 2). Interestingly, the prevalence of diabetes in medical records did not show significant difference across the three cohorts (Table 2).

Table 2. Prevalence of hypertension and diabetes across cohorts

Variable; n (%)	Vis (n=1,029)	Korčula (n=2,782)	Split (n=1,012)	*P*
Hypertension, medical records	354 (34.4)	944 (33.6)	263 (26.0)	<0.001
Hypertension, measured	465 (45.2)	901 (32.1)	282 (27.9)	<0.001
Diabetes, medical records	67 (6.5)	143 (5.1)	45 (4.4)	0.093
Diabetes, measured	169 (16.4)	442 (15.7)	78 (7.7)	<0.001

The analysis of the measured vs. diagnosed hypertension suggested that 14.4% of all subjects could be classified as incident (new) cases (Table 3). When taken within the diagnosed hypertension group, 60.8% of all subjects (949/1,561) were improperly treated (Table 3). The breakdown according to cohort indicated that Vis had the highest share of incident cases (19.4%) followed by Split (13.1%) and Korčula (13%) (Table 3) with the prevalence of incident cases being significantly higher in Vis (Chi-square=25.79; $P<0.001$). The prevalence of improperly treated subjects across cohorts showed a similar distribution with 74.9% in Vis, 56.7% in Korčula and 56.7% in Split (Chi-square=38.0; $P<0.001$, with significant difference driven by Vis vs. Korčula and Split).

Table 3. The analysis of measured vs. diagnosed hypertension

		Diagnosed hypertension (medical history **OR** use of hypertension-related medication)		
		Yes	No	Total
Measured hypertension (BP over 140 mmHg for systolic **OR** 90 mmHg for diastolic); n (%-*total*), entire sample	Yes	949 (19.6)	699 (14.4)	1,648
	No	612 (12.6)	2,590 (53.4)	3,202
	Total	1,561	3,289	4,850
Measured hypertension (BP over 140 mmHg for systolic **OR** 90 mmHg for diastolic); n (%-*total*), Vis	Yes	265 (25.8)	200 (19.4)	465
	No	89 (8.6)	475 (46.2)	564
	Total	354	675	1029
Measured hypertension (BP over 140 mmHg for systolic **OR** 90 mmHg for diast.); n (%-*total*), Korčula	Yes	535 (19.0)	366 (13.0)	901
	No	409 (14.5)	1,501 (53.4)	1,910
	Total	944	1867	2,811
Measured hypertension (BP over 140 mmHg for systolic **OR** 90 mmHg for diastolic); n (%-*total*), Split	Yes	149 (14.7)	133 (13.1)	282
	No	114 (11.3)	616 (60.9)	730
	Total	263	749	1,012

The analysis of diabetes in general had a similar pattern, but with even more inadequately treated subjects – 80% of diagnosed cases were inadequately treated (Table 4). Overall 10.6% of subjects were incident cases, with a significantly better situation in Split with 4.4% (Chi-square=47.91; $P<0.001$) and comparable percentages in Vis (12%) and Korčula (12.2%) (Table 4). The prevalence of improperly treated subjects across cohorts was 79.1% in Vis, 81.1% in Korčula and 77.8% in Split (Chi-square=0.28; $P=0.987$).

Table 4. The analysis of measured vs. diagnosed diabetes

		Diagnosed diabetes (medical history **OR** use of diabetes-related medication)		
		Yes	No	Total
Fasting serum glucose over 6.5 mmol/L **OR** HbA1c greater than 6.5%; n (%-*total*), entire sample	Yes	204 (4.2)	485 (10.0)	689
	No	51 (1.0)	4,110 (84.7)	4,161
	Total	255	4,595	4,850
Fasting serum glucose over 6.5 mmol/L **OR** HbA1c greater than 6.5%; n (%-*total*), Vis	Yes	53 (5.2)	116 (11.3)	169
	No	14 (1.4)	846 (82.2)	860
	Total	67	962	1,029
Fasting serum glucose over 6.5 mmol/L **OR** HbA1c greater than 6.5%; n (%-*total*), Korčula	Yes	116 (4.1)	326 (11.7)	442
	No	27 (1.0)	2,342 (83.3)	2,369
	Total	143	2,668	2,811
Fasting serum glucose over 6.5 mmol/L **OR** HbA1c greater than 6.5%; n (%-*total*), Split	Yes	35 (3.5)	43 (4.2)	78
	No	10 (1.0)	924 (91.3)	934
	Total	45	967	1,012

The regression model for prediction of the incident cases of hypertension suggested strong cohort-based differences, with the highest odds in Vis (Table 5). The same model indicates strong age-related risk increase, with a significant effect from the years of education – higher education was associated with reduced risk of becoming an incident case (Table 5). The model explained 14.7% of variance. The improperly treated hypertension model indicated even stronger cohort effect, again with Vis as the worst cohort, and comparable risks in Korčula and Split (Table 5). There was no strong age-related effect and no statistically significant effect regarding education. The percent of variance regarding improperly treated hypertension was 5.5%, amounting to a third of the variance from the incident hypertension model (Table 5).

Table 5. The logistic regression model predicting incident and improperly treated hypertension

	Incident hypertension		Improperly treated hypertension	
	P	OR (95% CI)	P	OR (95% CI)
Cohort				
Vis (*referent*)	<0.001	1.00	<0.001	1.00
Korčula	<0.001	0.67 (0.54-0.83)	<0.001	0.48 (0.36-0.63)
Split	0.033	0.74 (0.56-0.98)	0.001	0.55 (0.38-0.79)
Age group				
18-34 (*referent*)	<0.001	1.00	0.003	1.00
35-64	<0.001	4.21 (2.94-6.02)	0.354	1.57 (0.61-4.08)
65+	<0.001	12.79 (8.60-19.03)	0.092	2.29 (0.87-5.98)
Years of education	<0.001	0.93 (0.90-0.96)	0.169	0.98 (0.94-1.01)
Material status, subjective	0.328	0.93 (0.81-1.07)	0.989	1.01 (0.86-1.17)
Material status, indicator	0.128	1.03 (0.99-1.07)	0.284	0.98 (0.93-1.02)
R^2; %	**14.7**		**5.5**	

R^2 – percent of variance explained by the model

The logistic regression model predicting incident and improperly treated diabetes indicated different findings. There were no statistically significant differences between Vis and Korčula, while living in Split was associated with a reduced risk of being incidentally diagnosed with diabetes (OR: 0.50; 95% CI: 0.34-0.74) (Table 6). Both years of education (OR: 0.92; 95% CI: 0.89-0.95) and subjective estimate of material status (OR: 1.19; 95% CI:1.03-1.38) were significant predictors for incident diabetes, suggesting that it was more likely to be developed by those with lower education and higher socio-economic status (Table 6). Improperly treated diabetes had equal odds between all three cohorts, but was more likely to be developed by the middle-age group (OR: 6.73; 95% CI: 1.20-37.74) (Table 6). Interestingly, no other variables reached significance in this model. Similar to the hypertension model, the percent of variance for incident diabetes cases was about three times higher than for improperly treated diabetes.

Table 6. The logistic regression model predicting incident and improperly treated diabetes

	Incident diabetes		Improperly treated diabetes	
	P	OR (95% CI)	P	OR (95% CI)
Cohort				
Vis (*referent*)	<0.001	1.00	0.659	1.00
Korčula	0.210	1.17 (0.92-1.48)	0.958	1.02 (0.48-2.17)
Split	<0.001	0.50 (0.34-0.74)	0.449	0.67 (0.24-1.88)
Age group				
18-34 (*referent*)	<0.001	1.00	0.092	1.00
35-64	<0.001	8.39 (3.93-17.89)	0.030	6.73 (1.20-37.74)
65+	<0.001	16.25 (7.53-35.08)	0.063	5.14 (0.92-28.83)
Years of education	<0.001	0.92 (0.89-0.95)	0.738	1.02 (0.92-1.12)
Material status, subjective	0.020	1.19 (1.03-1.38)	0.095	1.57 (0.93-2.68)
Material status, indicator	0.945	1.00 (0.96-1.05)	0.966	1.00 (0.86-1.16)
R^2; %	**11.2**		**4.8**	

R^2 – percent of variance explained by the model

5. DISCUSSION

The results of this study show alarmingly high percentages of patients with hypertension and diabetes that are being improperly treated – 60.8% of patients with hypertension had elevated blood pressure levels at measurement, while 80% of people with diagnosed diabetes had elevated levels of HbA1c, suggesting the need for a systematic intervention across health care.

A study conducted in 2011-2012 in the US found every third adult to have high blood pressure. Nearly half (48.2%) of these subjects had poorly controlled hypertension. More than a third (36.2%) of those affected were not aware of their condition (42). Another study revealed that globally almost half (45.8%) of all diabetes cases in adults remain undiagnosed. Most of those cases (83.8%) were found in low and middle income countries (43).

Our findings regarding improperly treated hypertension were more pronounced in the island Vis with 74.9% of subjects with medical records of hypertension still having high blood pressure during our measurements, while in Split and Korčula this number only amounted to 56.7%. The situation with incident cases was better overall, only about 14% of all subjects could be considered as incident cases for hypertension and 10% for diabetes. However, our study revealed significant differences between the cohorts, Vis again in front with 19.4% of incident cases of hypertension compared to 13.1% in Split and 13% in Korčula. In the section of incident cases of diabetes Split achieved by far the best result with only 4.4% compared to 12% in Vis and 12.2% in Korčula. Interestingly, the numbers seemed to be nearly equally distributed throughout the cohorts in the case of improperly treated diabetes.

In order to uncover why the population of Vis had the highest numbers in regard to both incident cases and improperly treated cases of hypertension we must assume that age might have been a confounding factor. Furthermore, the studied population from Vis had the highest proportion of men, so supposedly sex was also a confounder. Numerous papers have found gender differences in incident cases of hypertension and diabetes. For example, a study from 2015 found that male subjects under 65 years of age had higher levels of hypertension compared to women of the same age. This was believed to have both biological and behavioral reasons (44). Another paper studying the age-related differences in antihypertensive medication adherence found a negative correlation between recent poor physical health and adherence (45).

The cohort-based differences revealed in our study are surely one of the things that requires more attention, especially having in mind the preamble of the Croatian health care laws, which aim to provide equal level of care for all people (46).

Admittedly, our figures are almost certainly an overestimation, as the patients could have had "white coat" syndrome or could have misreported being fasting at blood sample taking, suggesting that the real number of incident cases is probably lower than our results imply.

Interestingly, the percentages of variance explained by the model were about three times higher for both hypertension and diabetes in the incident model compared to the improperly treated model. These findings suggest that internal variables, such as years of education or socioeconomic status have more effect on the incident cases, while other external variables have more effect on improper treatment. This indirectly shows that the burden of improperly treated patients is more in the domain of health care than the individual.

Our model is admittedly over-simplified, but it suggests that the intervention towards incident cases should be population-based, while the improvement of the share of properly treated patients should be sought within the health care system itself. There is a need for further research to be conducted in order to identify system related factors that affect adherence.

The limitations of this study include a set of rather narrow data, lack of information on the GP, which could have explained a lot more variance due to possible differences between them. A retrospective cohort study with 6436 patients found great discrepancies in adherence to therapy depending on the treating physician, suggesting a link between health providers and patient adherence (47). Also, we are lacking a number of possible confounders, including disease-related behaviours, coping mechanisms, locus of control or similar estimates of behaviour.

Nevertheless, these results suggest the need for a substantial improvement of this situation, having in mind that hypertension and diabetes are two main chronic diseases that increase cardiovascular and all-cause morbidity and mortality.

6. CONCLUSION

1. The probability of having improperly treated hypertension was lower among examinees from Korčula and Split compared to Vis.
2. Subjects from Vis were the oldest and had the highest proportion of male examinees.
3. Vis inhabitants had the least years of education, lowest subjective social status and lowest material status.
4. Our results suggest a positive correlation between incident cases of diabetes and hypertension and living on Vis, older age and less years of education.

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8. SUMMARY

Objectives: The aim of this study was to identify individuals with undiagnosed diabetes/hypertension and those with known but poorly controlled diabetes/hypertension in a large population-based sample from Dalmatia. We further tried to determine characteristics and traits that were associated with a higher degree of adherence.

Materials and Methods: We accessed the data of all subjects recruited in the islands of Vis and Korčula, as well as those from the city of Split. The subjects were classified into four groups: (a) diagnosed, properly treated, (b) diagnosed, improperly treated, (c) incident - newly diagnosed and (d) healthy - undiagnosed. The statistical analysis was based on descriptive and analytic methods. Analysis of variance was used in the numeric data analysis for three cohorts. Chi-square test was used in the analysis of categorical variables. Logistic regression model was used in the final analytic step. All analyses were performed using SPSS v 21 with significance set at $P<0.050$.

Results: We found 14.4% of all subjects to be incident cases for hypertension. Within the diagnosed hypertension group, 60.8% of subjects were improperly treated. 80% of diagnosed diabetes cases were inadequately treated. 10.6% of subjects were found to be incident cases for diabetes. The regression model for prediction of the incident cases of hypertension revealed strong cohort-based differences, with the highest odds in Vis. We further found a strong age-related risk increase, with a significant effect from the years of education – higher education was associated with reduced risk of becoming an incident case. The improperly treated hypertension model indicated even stronger cohort effect, again with Vis as the worst cohort. Regarding diabetes there were no significant differences between Vis and Korčula, while living in Split was associated with a reduced risk to be an incident case (OR: 0.50). Our results suggest that those with lower education and higher socio-economic status were more likely to develop diabetes. Improperly treated diabetes was more likely to be developed by the middle-age group.

Conclusion: The probability of having improperly treated hypertension was lower among examinees from Korčula and Split compared to Vis. Our results suggest a positive correlation between incident cases of diabetes and hypertension and living on Vis, older age and less years of education.

9. CROATIAN SUMMARY

Naslov: Suradljivost bolesnika s dijabetesom i hipertenzijom

Ciljevi: Cilj ovog istraživanja bio je prepoznati osobe s dijagnozom šećerne bolesti ili povišenog krvnog tlaka te utvrditi jesu li one primjereno ili neprimjereno liječene. Dodatan cilj bio je istražiti obilježja ispitanika koji se pridržavaju svoje terapije i dobro kontroliraju bolest s onima koji imaju znakove bolesti unatoč korištenju terapije.

Materijali i metode: Korišteni su podatci ispitanika iz projekta 10.001 Dalmatinac, i to s otoka Visu i Korčule, kao i iz grada Splita. Ispitanici su bili svrstani u četiri skupine: (a) prisutna dijagnoza, bez znakova akutne bolesti, (b) prisutna dijagnoza, prisutni znakovi bolesti, (c) novodijagnosticirani slučaj te (d) zdravi ispitanici. Krvni tlak je mjeren dva puta u sjedećem položaju nakon 10 minuta odmora, a kao granične vrijednosti korištene su 140 mmHg za sistolički i 90 mmHg za dijastolički krvni tlak. Ispitanici sa serumskom razinom glukoze iznad 6,5 mmol ili razinom HbA1c iznad ove granične vrijednosti su bili svrstani u skupinu bolesnika sa šećernom bolesti. Statistička analiza temeljila se na opisnim i analitičkim metodama. Korišteni su hi-kvadrat, analiza varijance i logistička regresija. Sve analize provedene su korištenjem SPSS v 21 s razinom značajnosti postavljenom na $P < 0,050$.

Rezultati: 14,4% svih ispitanika su bili novodijagnosticirani slučajevi povišenog krvnog tlaka. Među njima, neprimjereno je bilo liječeno čak 60,8%. Za šećernu bolest taj postotak bio je i veći - čak 80% bolesnika nije imalo primjerene rezultate mjerenja razine šećera u krvi. Utvrđeno je da 10,6% ispitanika predstavlja incidentne slučajeve. Regresijski model za predviđanje incidentnih slučajeva hipertenzije pokazao je izrazite razlike među analiziranim populacijama, s najvećim rizikom na otoku Visu. Dob je bila važan prediktor modela, kao i razina obrazovanja. Model za šećernu bolest nije ukazivao na postojanje razlika među analiziranim pod-skupinama.

Zaključci: Rezultati ovog istraživanja pokazuju izražene razlike među analiziranim pod-skupinama i stvaraju osnovicu za izradu javnozdravstvene intervencije.

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